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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/424,247	10/30/2002	Francis Vanderbist	4068-0002-0P	7736

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1615

DATE MAILED: 10/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/424,247	VANDERBIST ET AL.	
	Examiner	Art Unit	
	Retford Berko	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 09 June 2004.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 14-38 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 14-38 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>6/9/04</u> . | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Acknowledgement: Applicant's amendment filed April 9, 2004 is acknowledged. The Information Disclosure Statement filed June 6, 2004 is also acknowledged.

Status of Claims

The status of the claims is as follows:

All previous claims, i.e. claims 1-13 were cancelled by the amendment.

Claims 14-38 are currently pending. All claims 14-38 were added as new claims following the amendment. The new claims necessitated a new search for prior art.

New Grounds of Rejections:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

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1. Claim 14-16 and 31 are rejected under 35 U.S.C. 102(e) as being anticipated by Cutie et al (US 6, 129, 905; filed August 13, 1997 and a continuation of 08/843, 811 that was filed April 21, 1997).

The claims are directed toward dry powder inhaler pharmaceutical composition comprising particulate pharmaceutically active ingredient and particulate beta-lactose excipients and a process of making said powder. The claims are also directed toward particle size of the drug and the beta-lactose excipient. According to the claims, the process for preparation of the beta-lactose excipients entails steps such as evaporation, crystallization, separation, washing, drying and sieving and redisolving.

As in claim 14-16, Patent '905 teaches particulate drug formulation for inhalation wherein the excipients is beta-lactose (col 10, example 14).

As in claim 15 and 16, Patent '905 teaches particles size of the drug as 100 microns.

As in claim 31; Patent '905 teaches a method of preparing particles of drug by mixing beta-lactose excipients with drug (col 7, lin 10-15, lin 50 and col 9, lin 30-65).

Claims 14-16 and 31 are anticipated by Patent '905.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

2. Claims 14-38 are rejected under 35 U.S.C.103(a) as being unpatentable over Sarlikiotis et al (US 6, 284, 287) in view of the combination of Ganderton et al (US 5, 376, 386), Cutie et al (US 6, 129, 905) and Tomkiewicz et al (Eur Respir J. 7(1): 81-87, 1994).

3. Claims 14-19 and 21-30 are directed toward the dry powder inhaler pharmaceutical composition comprising particulate pharmaceutically active ingredient and particulate beta-lactose excipients and a process of making said powder. The claims are also directed toward particle size of the drug and the beta-lactose excipients (50-250 microns, 100 and 160 microns) and rugosity of 1.9-2.4. The claims are further directed toward the particle size of the drug ingredient (0.5-6 microns) wherein the ratio of drug to excipients is 0.1/100 to 50/100) and wherein the drugs present include mucolytic agents (e.g. L-lysine N-acetylcysteinate), anti-inflammatory agents (e.g. budesonide), salbutamol and agents such as sodium cromoglycate.

Claims 20 and 31-38 are directed toward the method or process for preparing the powder composition wherein said process involves mixing of the beta-lactose excipients with drug having the physical parameters as in the claims already discussed for the composition. The other process steps involve evaporation, crystallization, separation, washing, drying and sieving and redisolving.

4. Sarlikiotis et al (Patent '287) meet the limitations of applicant's claims for the composition (i.e. claims 14-19 and 21-30) in that Patent '287 discloses a powder formulation comprising active compounds (e.g. steroids, budesonide, salbutanol and disodium cromoglycate) and excipients (e.g. lactose, maltose and cyclodextrin)---col 3, lin 25-50, col 4, lin 5-10 and col 5, lin 60-65, continuing to col 6, lin 30-60). According to Sarlikiotis et al, the particle size of the excipients is 200-1000 microns and the particle size of the drug is 0.1-10 microns while the rugosity is greater than 1.75 (col 7, lin 10-30). Further, Patent '287 also meets the limitations of applicant's claims for the process of making the composition (i.e. claims 20 and 31-38) in that Patent '287 the preparation of the formulation (col 4, lin 38-55).

5. Patent '287 does not disclose the use of beta-lactose as excipients in the formulation, does not disclose the use of L-lysine N-acetylcysteinate and does not provide a rational for rugosity values chosen for the formulation.

Ganderton et al (Patent '386) disclose pharmaceutical excipients useful in dry powder inhalation (abstract). According to Ganderton et al, the particle size of the lactose used as excipient in inhaler formulation was 60-90 micrometers (col 5, lin 30), that the rugosity of conventional excipients is at least 1.96 and generally greater than 2.0 (col 1, lin 60-65). This disclosure is consistent with the disclosures of particle size and rugosity for drug particles and excipients in the formulation (Sarlikiotis et al; Patent '287, col 7, lin 10-30).

Cutie et al (Patent '905) disclose particulate drug formulation for inhalation wherein the excipients is beta-lactose (example 1, col 6, lin 10-15 and example 14, col 10, lin 55-60), discloses particle size of the drug (col 5, lin 10-15) and discloses the particle size of the

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excipients sugar (col 4, lin 65). Patent '905 further provides a method for making the formulation (col 7, lin 10-15, lin 50 and col 9, lin 30-65).

Tomkiewicz et al (Eur Respir J. 7(1): 81-87, 1994) disclose applicant's limitation not provided by the above cited prior art references--the use of L-lysine N-acetylcysteinate, also known as N-acetylcysteine L-lysinate or Nacystelyn). Tomkiewicz et al disclose the use of Nacystelyn as a drug useful for removing accumulated mucus secretions from the lung in dogs (abstract).

One of ordinary skill in the art would have been motivated to prepare particulate formulations comprising active ingredients and excipients for inhalation for treatment of respiratory diseases such as asthma as disclosed in the prior art cited. By using the combination of methods disclosed in the prior art cited, one of ordinary skill would expect reasonable level of success in obtaining a composition having the necessary effective drugs and physical characteristics such as particle size rugosity; such physical characteristics permitting the composition to be beneficial in improving mucus rheological properties and thereby increase the efficiency of removing accumulated secretions from the lung airways for asthma patients and patients with other respiratory ailments. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill at the time it was made.

The following prior art references are cited for the record as pertinent to applicant's claims but are not relied upon in for making the rejections in this office action:

(a) Tomkiewicz et al (Pulm Pharmacol. 1995 Dec; 8(6):259-65). The reference teaches N-acetylcysteine L-lysinate and acetylcysteine as useful mucolytic agents in mammals. The

reference supports the reference used by the same author as discussed above. The reference is not being used as it will only be cumulative evidence.

(b) Stevenson et al (US 4, 199, 578) discloses a pharmaceutical composition for inhalation with particle size below 400 micrometers wherein the carrier is lactose. (col 4, lin 20-60, col 5, lin 10-25 and col 6, lin 15). The reference is not used because it does not specifically mention the use of beta-lactose as excipients.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Retford Berko** whose telephone number is 571-272-0590. The examiner can normally be reached on M-F from 8.00 am to 5.30 pm

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Thurman K Page**, can be reached on 571-272-0602.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,

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SUPERVISORY PATENT EXAMINER
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